European Commission Approves Prolia® (denosumab) for Patients With Glucocorticoid-Induced Osteoporosis

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Third Indication in Europe for Prolia for the Treatment of Patients at Increased Risk of Fractures

THOUSAND OAKS, Calif., June 8, 2018 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the European Commission (EC) has approved a new indication for Prolia® (denosumab) for the treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture. The EC approval is based on the positive results of a Phase 3 study that evaluated the safety and efficacy of Prolia compared with risedronate in patients receiving glucocorticoid treatment.[1]

"We are pleased that today's EC approval provides physicians with a new treatment option for bone loss associated with the use of glucocorticoid medications," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "As a leader in bone health with more than 20 years of osteoporosis research experience, we believe that Prolia can address a critical treatment need for patients with glucocorticoid-induced osteoporosis in Europe and globally."

"Long-term glucocorticoid therapy is associated with a rapid and early decline in bone mineral density and increase in fracture risk," said Professor Dr. Willem F. Lems, researcher and rheumatologist, VU University Medical Centre, Amsterdam. "This approval provides a new treatment option to effectively counter the detrimental effects of glucocorticoid therapy on bone in patients at increased risk of fracture."

The EC approval is supported by a Phase 3 randomized, double-blind, double-dummy, active-controlled study evaluating the safety and efficacy of Prolia compared with risedronate in patients receiving glucocorticoid treatment.[1] The study included two patient groups: those on sustained glucocorticoid therapy and those newly initiating glucocorticoid therapy. The study met the primary endpoint (percent change from baseline in lumbar spine bone mass density [BMD] at 12 months, assessing non-inferiority) and all secondary endpoints (the percent changes from baseline in lumbar spine and total hip BMD at 12 and 24 months, assessing superiority).

In the glucocorticoid-continuing subpopulation, Prolia demonstrated a greater increase in lumbar spine BMD compared to risedronate at one year (Prolia 3.6 percent, risedronate 2.0 percent; $p<0.001$) and two years (Prolia 4.5 percent, risedronate 2.2 percent; $p<0.001$). In the glucocorticoid-initiating subpopulation, Prolia demonstrated a greater increase in lumbar spine BMD compared to risedronate at one year (Prolia 3.1 percent, risedronate 0.8 percent; $p<0.001$) and two years (Prolia 4.6 percent, risedronate 1.5 percent; $p<0.001$).

In addition, compared with risedronate, Prolia demonstrated significantly greater mean percent increases in BMD from baseline at one and two years at the total hip, femoral neck and trochanter in both the glucocorticoid-continuing and glucocorticoid-initiating subpopulations. Adverse events and serious adverse events were similar between treatment groups and consistent with the known safety profile of Prolia. No serious adverse events were reported with a subject incidence of two percent or greater in either treatment group.

The U.S. Food and Drug Administration (FDA) approved the expanded indication of Prolia for the treatment of osteoporosis associated with newly initiating or sustained systemic glucocorticoid therapy in men and women at high risk of fracture on May 18, 2018.

About Glucocorticoid-Induced Osteoporosis (GIOP)

GIOP is the most common form of secondary osteoporosis.[2] However, the proportion of patients that qualify for GIOP diagnosis and intervention is small and depends on the level of exposure to glucocorticoid medications.[3,4] In addition, a significant proportion of the patients treated long-term with glucocorticoid medications are already diagnosed with postmenopausal osteoporosis or treated with osteoporosis medications. Importantly, at similar levels of BMD, postmenopausal women taking glucocorticoids have considerably higher risk of fracture compared with postmenopausal nonusers of glucocorticoids.[5] The most frequent chronic inflammatory diseases associated with long-term glucocorticoid use are chronic obstructive pulmonary disorder (COPD), asthma and rheumatoid arthritis.[6] In an European Union (EU) study, 30 to 40 percent of patients on long-term glucocorticoid treatment had radiographic evidence of vertebral fractures.[6]

About Prolia® (denosumab)

Prolia is the first approved therapy that specifically targets RANK Ligand, an essential regulator of bone-removing cells (osteoclasts). Prolia is approved and marketed in over 80 countries worldwide.

Prolia is approved in the U.S. for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In the U.S., Prolia is also approved for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. Prolia is also indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer and in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer in the U.S. Prolia was approved by the FDA on May 18, 2018, as a treatment for patients with glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least six months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

Prolia is approved in the EU for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women, Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

In the EU, Prolia is also approved for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.

Prolia is also approved in the EU for the treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

Prolia is administered as a single subcutaneous injection of 60 mg once every six months. Please see the Important Safety Information below.

EU Important EU Product Information

Calcium and Vitamin D supplementation
Adequate intake of calcium and vitamin D is important in all patients.

Precautions for use

Hypocalcaemia
It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment (see section 4.8 for symptoms) calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.

In the post-marketing setting, severe symptomatic hypocalcaemia has been reported (see section 4.8), with most cases occurring in the first weeks of initiating therapy, but it can occur later.

Skin infections
Patients receiving Prolia® may develop skin infections (predominantly cellulitis) leading to hospitalisation (see section 4.8). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Osteonecrosis of the Jaw (ONJ)
ONJ has been reported rarely in patients receiving Prolia® for osteoporosis (see section 4.8).

The start of treatment/new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Prolia® administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur
Atypical femoral fractures have been reported in patients receiving denosumab (see section 4.8). Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterise these events. Atypical femoral fractures have also been reported in patients with certain co-morbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of Prolia® therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit-risk assessment. During denosumab-treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.

Long-term antiresorptive treatment
Long-term antiresorptive treatment (including both denosumab and bisphosphonates) may contribute to an increased risk for adverse outcomes such as osteonecrosis of the jaw and atypical femur fractures due to significant suppression of bone remodelling (see section 4.2).

Concomitant treatment with other denosumab-containing medicinal products
Patients being treated with Prolia® should not be treated concomitantly with other denosumab-containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumours).

Renal impairment
Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients, see above.

Dry natural rubber
The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Warnings for excipients
This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg i.e. essentially 'sodium-free'.

U.S. Important Safety Information

Contraindications
Prolia® is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia®. Prolia® is contraindicated in women who are pregnant and may cause fetal harm. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®. Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling and urticaria.

Same Active Ingredient
Prolia® contains the same active ingredient (denosumab) found in XGEVA®. Patients receiving Prolia® should not receive XGEVA®.

Hypersensitivity
Clinically significant hypersensitivity including anaphylaxis has been reported with Prolia®. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of Prolia®.

Hypocalcemia
Hypocalcemia may worsen with the use of Prolia®, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended within 14 days of Prolia® injection. Adequately supplement all patients with calcium and vitamin D.

Osteonecrosis of the Jaw (ONJ)
ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia®. An oral exam should be performed by the prescriber prior to initiation of Prolia®. A dental examination with appropriate preventive dentistry is recommended prior to treatment in patients with risk factors for ONJ such as invasive dental procedures, diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders. Good oral hygiene practices should be maintained during treatment with Prolia®. The risk of ONJ may increase with duration of exposure to Prolia®.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia® should be considered based on individual benefit-risk assessment.

Atypical Femoral Fractures
Atypical low-energy, or low trauma fractures of the shaft have been reported in patients receiving Prolia®. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with anti-resorptive agents.

During Prolia® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be evaluated to rule out an incomplete femur fracture. Interruption of Prolia® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment
Following discontinuation of Prolia® treatment, fracture risk increases, including the risk of multiple vertebral fractures. New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of Prolia®. Prior vertebral fracture was a predictor of multiple vertebral fractures after Prolia® discontinuation. Evaluate an individual's benefit/risk before initiating treatment with Prolia®. If Prolia® treatment is discontinued, consider transitioning to an alternative anti-resorptive therapy.

Serious Infections
In a clinical trial (N=7,808) in women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia® group than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract and ear were more frequent in patients treated with Prolia®.

Endocarditis was also reported more frequently in Prolia®-treated patients. The incidence of opportunistic infections and the overall incidence of infections were similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on Prolia®, prescribers should assess the need for continued Prolia® therapy.

Dermatologic Adverse Reactions

In the same clinical trial in women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema and rashes occurred at a significantly higher rate with Prolia® compared to placebo. Most of these events were not specific to the injection site. Consider discontinuing Prolia® if severe symptoms develop.

Musculoskeletal Pain
Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking Prolia®. Consider discontinuing use if severe symptoms develop.

Suppression of Bone Turnover
In clinical trials in women with postmenopausal osteoporosis, Prolia® resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment are unknown. Monitor patients for these consequences, including ONJ, atypical fractures, and delayed fracture healing.

Adverse Reactions
The most common adverse reactions (>5% and more common than placebo) in women with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions (> 5% and more common than placebo) in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. Pancreatitis has been reported with Prolia®.

In women with postmenopausal osteoporosis, the overall incidence of new malignancies was 4.3% in the placebo group and 4.8% in the Prolia® group. In men with osteoporosis, new malignancies were reported in no patients in the placebo group and 4 (3.3%) patients in the Prolia® group. A causal relationship to drug exposure has not been established.

The most common adverse reactions (>3% and more common than active-control group) in patients with glucocorticoid-induced osteoporosis were: back pain, hypertension, bronchitis, and headache. The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia® in patients with bone loss receiving ADT for prostate cancer or adjuvant AI therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. Additionally, in Prolia®-treated men with nonmetastatic prostate cancer receiving ADT, a greater incidence of cataracts was observed.

Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

For more information, please see the Prolia® Prescribing Information and Medication Guide.

About Amgen
Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

Forward Looking Statements
This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and current reports on Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products, including our devices, after they are on the market.

Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax

liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities, including in Puerto Rico, and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of our systems and our data. Our stock price is volatile and may be affected by a number of events. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.

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